EDITORIAL REVIEW

Infectious complications after burn injury

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Since the inception of organized burn care nearly 50 years ago, infections complicating the care of thermally injured patients have been recognized as a major source of morbidity and mortality. The control of invasive infection and burn wound sepsis and improvements in the general care of these critically ill patients have resulted in unsurpassed survival; even so, infection remains the most frequent cause of death in these severely injured patients.

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Introduction

Infectious complications continue to be the predominant determinant of outcome in thermally injured patients. Improvements in the general care of these critically ill patients and control of invasive infection and burn wound sepsis through the use of effective topical antimicrobial agents and timely excision and grafting have resulted in the survival of more patients who previously would have died soon after being burned.

Coincident with improvements in survival and prolongation of the hospital course of nonsurvivors, changes in the epidemiology of infection have occurred, resulting in a predominance of true fungi, yeast, and multiple antibiotic resistant bacteria as the causative agents of nosocomial infections. Control of the bacterial burn wound flora has been associated with a relative increase of infections in other sites, predominantly the lungs, as principal causes of morbidity and mortality.

Additionally, prolongation of the hospital course of nonsurvivors, most of whom die as a result of overwhelming infection or multiple system organ failure, has focused interest on the pathogenesis of the systemic inflammatory response syndrome and the role of systemic cytokine liberation, intestinal bacterial translocation, and polymorphonuclear leukocyte activation in the cause of multiple system organ failure.

Further characterization of the host response to thermal injury may identify potentially deleterious processes or pathways that contribute to an exaggerated systemic inflammatory response. Such information can be used to formulate selective pharmacologic interventions that ameliorate an uncontrolled inflammatory response or prevent its occurrence. This process recapitulates the events that led to the description of invasive bacterial burn wound infection and the development of effective topical antimicrobial agents, essentially eliminating bacterial burn wound infection as a clinical problem.

Epidemiology of infection

During the past 4 decades, the prophylactic use of effective topical antimicrobial agents such as mafenide acetate burn cream, silver sulfadiazine burn cream, and dilute (0.5%) silver nitrate soaks has become routine, and prompt excision and early closure of the burn wound have become standard practice; at the same time, the occurrence of invasive burn wound infection and its related mortality have significantly diminished. Other factors that have contributed to the decrease in burn wound infections are listed in Table 1.

Table 1. Factors associated with decreasing incidence of burn wound infection.

Effective topical antimicrobial therapy.
Timely excision of burn wounds.
Availability of effective biologic dressings.
Improved burn wound monitoring.
Cohort isolation techniques.
Improved general care.

In a recent large series [1], in which the causes of mortality in thermally injured patients were reviewed, wound infection accounted for only 5.1% of infection-related deaths between 1987 and 1991, compared with 25.5% in 1979. Additionally, the initiation of single-bed isolation of seriously burned patients was associated with an unchanged incidence of colonization of the burn wound by *Pseudomonas aeruginosa*; colonization was, however,

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significantly delayed, when compared with a historical cohort (25 days after the burn, compared with 15 days) [2]. *Pseudomonas* pneumonia, invasive burn wound infection, and bacteremia each occurred at a decreased frequency and longer after the burn when this isolation technique was used with a rigorous microbial surveillance program and strict environmental infection control practises.

Nonbacterial infection

Longer survival of patients whose wounds remain open, either because of the extent of the burn or because of complications that necessitate the use of broad-spectrum antibiotics, increases the probability that organisms causing colonization or infection will be yeasts, fungi, or multiple antibiotic resistant bacteria. The moist, protein-rich, avascular eschar of a burn wound creates an excellent microbial culture medium into which parenterally administered antibiotics penetrate poorly, if at all, and thus have no effect on the rapid bacterial colonization in the burn wound.

Topical agents effectively control the initially sparse, predominately Gram-positive burn wound flora; in patients in whom prompt wound closure cannot be accomplished, however, the colonizing flora not only of the burn wound but also of the respiratory, gastrointestinal, and urinary tracts are often replaced by nosocomial Gram-negative organisms and nonbacterial opportunists.

In a recent review of 2114 thermally injured patients admitted to our institution [3], fungal wound infection occurred in 141 patients, whereas bacterial wound infection was documented in only 68 patients. In patients in whom the causative organism could be identified by microscopic morphologic appearance or culture recovery from tissue samples, filamentous fungi and *Candida* species were present in 82% and 18% of specimens, respectively. *Aspergillus* and *Fusarium* species were recovered in 68% of specimens, whereas *Rhizopus* and *Mucor* species were detected in only 9.1% and *Microspora* and *Alternaria* species in fewer than 5% each. Thus, fungi have replaced bacteria as the most common microbes causing invasive burn wound infection in this series.

Histopathologic identification of fungal invasion of viable subeschar tissue in a wound biopsy specimen should mandate prompt local surgical debridement of all involved tissue. Parenteral administration of amphotericin B should be started in patients who exhibit spread of fungal infection beyond the confines of the burn wound or have evidence of microvascular or lymphatic invasion detected by wound biopsy. Parenteral treatment with fluconazole and topical antifungal therapy have not been proved to be effective in this setting.

The exact relationship of the administration of parenteral antibiotic therapy in burned patients to the emergence of fungi as the most common pathogens causing burn wound infection is unknown; these 'opportunistic' infections of the burn wound, however, have been associated with the reduced incidence of Gram-negative burn wound infection brought about by the use of effective topical chemotherapeutic agents. To prevent or minimize the emergence of multiple antibiotic resistant bacteria and nonbacterial pathogens, strict criteria for parenteral antibiotic use should be followed, and empiric antibiotic therapy for 'sepsis' in the absence of an identified source should be avoided.

Viral infections have also been recognized with increasing frequency in burned patients. At our institution, herpes simplex virus type 1, the most frequently identified virus causing infections, was identified as the cause of infection of the airway in nine patients and of the burn wound in five patients during a recent 6-year period [4••]. Cytomegalovirus infections of the airway were identified in six patients during the same period.

In a recent prospective study of cytomegalovirus seroconversion in burned patients [5], cytomegalovirus antibody titer increased more than fourfold in 31 out of 87 patients but appeared to have no effect on outcome.

Clinical manifestations of indolent infection, such as persistent temperature elevation, hepatitis, and lymphocytosis, suggest a viral origin and, in the absence of an identifiable bacterial source of infection, speak for the withholding of antibacterial agents, which would be ineffectual. The administration of antiviral agents such as adenine arabinoside or ganciclovir is indicated in patients with systemic viral infection and progressive deterioration.

Methicillin-resistant strains of *Staphylococcus aureus*

Antibiotic-resistant bacteria of special note and of much controversy are the methicillin-resistant strains of *S. aureus*. The strains that are principally resistant to penicillinase-resistant penicillins and aminoglycosides are increasingly common nosocomial isolates. Since the 1960s, these strains have been treated and reported as if they were distinct pathogens with more virulence than other methicillin-sensitive *S. aureus* strains. Clearly, the emergence of antibiotic-resistant organisms is of concern, and reasonable efforts should be made to reduce this occurrence; the unique concern, however, about methicillin-resistant strains in particular, above and beyond concern for *S. aureus* infection in general, that has caused temporary closure of care facilities and restriction of patient movement among levels of care must be weighed against the clinical and economic value of these added control practices.

In a unique report [6••], the virulence and pathologic significance of methicillin-resistant *S. aureus* strains compared with methicillin-sensitive strains causing infections in burned patients were evaluated. Colonization with any *S. aureus* was identified in 658 burned patients, treated during a 6-year period. In 319 of the patients, colonization by methicillin-resistant *S. aureus* was identified. A total of 253 staphylococcal infections occurred in

178 patients. Fifty-eight per cent of the infections were pulmonary and 38% were bacteremic. In 58 of the 178 patients (32.6%), infections were caused by methicillin-resistant *S. aureus*.

A severity index based on multiple logistic regression analysis of mortality in thermally injured patients was used to compare outcomes in patients infected by methicillin-resistant and methicillin-sensitive strains of *S. aureus* [6••]. In both groups, all patients were treated with vancomycin, and no differences in the observed and predicted mortality were found between groups. These results seriously questioned the need for unique precaution, isolation, or treatment in patients with methicillin-resistant infection. Nevertheless, these concerns persist and continue to appear in the medical literature [7].

The availability of vancomycin in a generic formulation and its efficacy with twice-daily dosing regimens have increased its economic appeal in the treatment of staphylococcal infections. Additionally, the newer formulations appear to be associated with less ototoxicity and nephrotoxicity than previously reported. The main concern related to frequent use of vancomycin is the possible development of vancomycin-resistant *S. aureus*, prompted by the recent recognition of vancomycin-resistant strains of *Enterococcus* species. The clinical development of vancomycin-resistant staphylococcal strains, however, is yet to be reported. To avoid inappropriate prescription of this and other antibiotics, strict criteria for antibiotic use based on the prevalence of resistant organisms at individual institutions and for diagnosing specific infections in burned patients should be adopted at each burn center.

Pneumonia

The improved survival of patients with massive burns has been associated with a relative increase in infections in sites other than the burn wound as principal causes of morbidity and death [4••]. Pneumonia is now the most frequent septic complication after thermal injury, and, as the incidence of invasive burn wound infection has decreased, bronchopneumonia has surpassed hematogenous pneumonia as the predominant form. Other factors contributing to this epidemiologic change are listed in Table 2.

Table 2. Factors associated with emergence of bronchopneumonia.

Decreased incidence of burn wound infection.
Decreased incidence of suppurative thrombophlebitis.
Prolonged intubation of airway and gastrointestinal tract.
Perioperative antibiotic use.
Increased numbers of patients with inhalation injury.
Excessive fluid resuscitation.

In a review encompassing a recent 5-year period at our burn center [8], pneumonia occurred in 169 out of 998 burned patients who were admitted. In 91 of the 166 fatally burned patients cared for during that period, pneumonia was present, and it was considered to be the primary cause of death in half of the patients who died.

The relative increase in the frequency of airborne pneumonia may also be, in part, attributed to improved survival in patients with severe smoke inhalation injury. Rue *et al.* [9••], using a logistic regression-derived mortality predictor based on patient age and extent of burn, recently compared the contemporary co-morbidity of inhalation injury and pneumonia with an historic cohort previously reported from the same institution [10]. Patients in the more recent period had a significantly lower mortality than predicted (29.4% compared with 41.4%). Patients with inhalation injury found on bronchoscopy, which was associated with a more severe injury, showed some improvement in outcome from that predicted (38.3% compared with 50.2%), but the rate of pneumonia was not different between cohorts.

A subset of 61 patients treated with high-frequency percussive ventilation was compared with patients treated with conventional volume-controlled ventilation [9••]. Despite similar age, burn size, and duration of intubation, the incidence of bronchopneumonia was markedly reduced, occurring in only 29.3% of the patients treated with percussive ventilation, compared with 52.3% of conventionally ventilated patients. Additionally, mortality was significantly less in patients treated with percussive ventilation than in the conventionally ventilated patients (16.4% compared with 42.7%) and significantly less than that predicted from the mortality predictor (16.4% compared with 40.9%).

In this study [9••], the combined effects of general improvement in care of all burned patients and the prevention of pneumonia by high-frequency percussive ventilation were shown to reduced mortality, compared with patients with pneumonia, and it significantly affected the survival of all patients with inhalation injury. This ventilatory mode appeared to have the beneficial therapeutic effect of facilitating the removal of endobronchial secretions and cellular debris while ventilating at airway pressures lower than those applied with conventional ventilation. Such effects interrupted the usual pathologic sequelae of severe inhalation injury and prevented or minimized small airway obstruction, distal atelectasis, progressive barotrauma, and pneumonia.

Hematogenous pneumonia is now encountered more rarely than bronchopneumonia and usually occurs later in the hospital course. Remote septic foci such as invasive wound infection, endocarditis, or suppurative thrombophlebitis are common causes. The radiographic hallmark is a solitary nodular pulmonary infiltrate, but progression to multiple nodular infiltrates throughout the lungs may occur. All possible sites of infection must be evaluated if a characteristic nodular pulmonary infiltrate appears, and the primary infection must be identified and treated. The pneumonic process is treated by sys-

temic administration of antibiotics directed against the causative organism and ventilatory support as needed.

In addition to the relative change in frequency of pneumonia, the predominant organisms causing pneumonia in burned patients have changed markedly during the past decade. In 1982, *P. aeruginosa* was considered the causative organism in 32% of the pneumonias occurring that year and *S. aureus* the causative organism of only 24%. In 1989, *S. aureus* was identified as the cause of 48% of pneumonias and *P. aeruginosa* the cause of merely 16% after burn injury. A similar trend in the emergence of Gram-positive organisms as the predominant flora responsible for pneumonia and other infections after burns has been documented at other institutions [11,12].

Infections at other sites

The control of invasive burn wound infection and the overall decrease in incidence of pneumonia have been associated with a relative increase in infections in other sites; the actual number of these infections, however, has decreased from previous years: suppurative thrombophlebitis is an example. At our institution, the incidence of suppurative thrombophlebitis decreased from 6.9% of patients treated during 1969 and 1970 to 1.4% during 1977 and 1978. From the middle of 1982 to December 1990, only 16 cases in 2268 burned patients were documented (0.71%) [4••]. Strict cannula discipline that limits cannula residence at a single site to a maximum of 72 h and the current approach to wound care have contributed significantly to the marked decline of this infection. In recent years, much like colonization of the respiratory tract, staphylococci have replaced Gram-negative organisms as the predominant cause of suppurative thrombophlebitis, and nonbacterial pathogens have emerged as causative organisms. Early diagnosis and prompt surgical excision of the involved vein before hematogenous dissemination of the infecting organisms reduces the morbidity and mortality associated with this complication.

Acute infective endocarditis is an infrequent but well described site of infection in burned patients that has occurred in 1.3% of patients in recent years. Burn wound manipulation, prolonged intravenous cannulation, and septic thrombophlebitis are the most common sources of bacteria producing this complication. Preventive measures include effective topical antimicrobial therapy, timely excision and closure of the burn wound, and early discontinuation or frequent replacement of intravenous cannulae. *S. aureus* is the most common causative organism, and the right side of the heart is most frequently affected. Recurrent staphylococcal bacteremia in a burned patient with sepsis and no other apparent identifiable source of infection should suggest the diagnosis; heart murmurs are often difficult to diagnose in hyperdynamic, tachycardic patients. Transesophageal echocardiography is the preferred examination to detect valvular lesions. Systemic maximal-dose antibiotic therapy is directed against the causative organism and continued for 6 weeks after the last positive blood culture.

The occurrence of paranasal sinusitis and infections of the urinary tract are related to the presence of the foreign materials of the tubes, cannulae, and catheters placed to gain access to the alimentary tract, airway, or urinary bladder, respectively. The incidence of both of these infections increases with the duration of cannulation, arguing for prompt removal of the catheters for effective prevention of these infections.

In a study of sinusitis in transnasally intubated burned patients [13], eight out of 22 patients who were intubated for more than 7 days and underwent computed tomographic scan of all paranasal sinuses, with timing dictated by the patient's clinical condition, had findings consistent with sinusitis. Removal of all nasal tubes, application of topical nasal decongestants, and administration of culture-specific antibiotics were successful in treating the infection in all but one patient.

In association with the changes in burn wound care and patient management, the incidence of all infections, including bacteremia in burned patients, has also decreased. The increased mortality associated with Gram-negative bacteremia is not observed with Gram-positive bacteremia [14]. In addition, the present mortality associated with Gram-negative bacteremia usually caused by normal host flora is significantly less than that caused in the past by endemic infecting strains that were often resistant to multiple antibiotics [2].

The emergence of Gram-positive organisms as the predominant flora has contributed to a lessening in the impact of infection. The virulence of *S. aureus*, however, may be strain-specific. Bacteremia resulting from strains of *S. aureus* possessing the gene for the production of toxic shock syndrome toxin-1 has been associated with episodes of unexplained profound hemodynamic instability in several burned patients treated by us and described by others [15,16]. This gene, however, has been identified in *S. aureus* strains recovered from patients with various infections, bacteremia, or wound colonization without evidence of profound physiologic alteration.

In burned patients with staphylococcal infections who manifest hemodynamic instability that responds poorly to treatment and that is out of proportion to that usually encountered in Gram-positive infections, the diagnosis of a variant of toxic shock syndrome should be considered. Acute management first requires aggressive intravenous fluid resuscitation to regain hemodynamic stability. Vancomycin should be administered intravenously unless the organism is known to be sensitive to methicillin, in which case a beta-lactamase-resistant antistaphylococcal antibiotic such as nafcillin may be given.

An antitoxin to the toxic shock syndrome toxin-1 is not clinically available. The prevalence of antibodies against the toxin is more than 90% in the general population, and nearly all patients with toxic shock syndrome related

to menstruation have had undetectable antibodies at onset of the disease. Although this relationship has not been confirmed in burned patients with staphylococcal infections and clinical evidence of toxic shock syndrome, the isolation of a strain of *S. aureus* that produces the toxic shock syndrome toxin-1 and the absence of circulating antibodies to the toxin may establish the diagnosis.

Systemic inflammatory response

Prolongation of the time until death of nonsurviving burned patients and the overall reduction in the number of patients succumbing to infections have generated an increased awareness of the occurrence of multiple system organ failure and the systemic inflammatory response syndrome. Consequently, studies of the pathogenesis of systemic inflammation have markedly proliferated, with special emphasis on identifying important causal factors and mechanisms.

Cytokines

The cellular response to injury and infection has been associated with systemic liberation of cytokines such as tumor necrosis factor α, interleukin-1β, and interleukin-6, and these cytokines have been extensively studied in various inflammatory diseases. The contributions of these cytokines to the initiation and perpetuation of the hypermetabolic state after burns and the host response to infection have recently been described [17,18]. In serial plasma samples obtained from 27 thermally injured patients, interleukin-1β, interleukin-6, and tumor necrosis factor α were measured by enzyme-linked immunosorbent assay, and correlations between core temperature and the presence or absence of infection were assessed. Interleukin-1β responded modestly to injury alone but showed little response to infection, whereas interleukin-6 and tumor necrosis factor-α levels were increased in severely infected patients compared with patients who remained free of infection. Interleukin-6 and interleukin-1β were also positively correlated with increases in core temperature. These results suggest that, in thermally injured patients, the observed alterations in cytokine concentrations may represent the effect rather than the cause of infection.

Bacterial translocation

The concept that the gut plays a central role in the initiation and maintenance of a persistent catabolic state in severely injured patients has gained substantial popularity. Severe injury has been clearly associated with breakdown of gut mucosal integrity in animals and humans. Intestinal permeability has been shown to be increased shortly after injury [19] and increased before and during episodes of sepsis [20]. Endotoxin has been identified in the blood of burned patients within hours of injury, but no direct proof has been found that the endotoxin originates in the gut [21].

In a recent prospective, randomized clinical study of 76 burned patients [22••], half of the patients were given intravenous polymyxin B for 1 week after the burn in doses designed to neutralize circulating endotoxin. The reduction in plasma endotoxin concentration compared with controls was statistically significant, although no reductions in interleukin-6 levels, Baltimore sepsis scores, or mortality were seen.

In recent clinical studies evaluating portal vein bacteremia [23] and the presence of bacteria in mesenteric lymph nodes [24] after mechanical trauma, investigators have also failed to substantiate the occurrence of significant bacterial translocation in humans. These recent studies seriously question whether alteration in intestinal permeability results in infection or represents only an epiphenomenon; the significance of bacterial translocation in the pathogenesis of clinical infection or systemic inflammation must also be questioned because of the lack of clinically significant bacteremia and endotoxemia in patients.

Granulocyte response

Burn injury elicits a response from the immune system that is proportional to the extent of the burn and that causes impaired function in some cells while sensitizing other cells such that a second insult induces an exaggerated and prolonged response. The metabolic products of activated leukocytes such as cytokines and reactive oxygen species may act beneficially to enhance host resistance or deleteriously to depress remote organ function through an overwhelming systemic inflammatory response. Although the complexity of the leukocyte response to burn injury has not allowed formulation of a unifying hypothesis other than that of global immunosuppression, recent studies have shown that, particularly in the case of granulocytes, certain characteristics once thought to represent hypofunction of polymorphonuclear leukocytes were actually due to systemic activation of these cells.

The classic observations documenting defects in chemotaxis, phagocytosis, bactericidal capacity, and superoxide and hydrogen peroxide production in granulocytes of thermally injured patients have been interpreted as evidence of dysfunction in these cells. Conversely, the concept of systemic activation of neutrophils after thermal injury has been supported in the recent literature. The historical development of the theories and evidence of polymorphonuclear leukocyte activation are thoroughly covered in a recent review by Cioffi *et al.* [25••].

In a recent study by the same authors [26], the effect of thermal injury on the oxidative potential of granulocytes serially collected from burned patients was evaluated by a fluorescent technique. Unstimulated granulocytes from burned patients showed a significantly higher baseline

activity than did unstimulated cells from controls. The granulocytes from burned patients also displayed greater than normal oxidase activity after in-vitro stimulation by phorbal myristate acetate, suggesting in-vivo activation and priming for an exaggerated response to a second insult.

Other evidence for in-vivo neutrophil activation has been reported by Dobke *et al.* [27], who demonstrated that the resting oxygen uptake of neutrophils was significantly increased in burned patients, compared with controls.

The 'second hit' concept, in which specific priming and activation sequences are postulated to result in significant in-vivo tissue injury, has recently been proposed on the basis of laboratory studies in a murine model [28]. In rats, low-dose lipopolysaccharide administration caused a priming of neutrophils that was partially mediated by platelet activating factor. Subsequent exposure of those cells to a non-injurious dose of f-met-leu-phe resulted in significant pulmonary injury. The organ injury was blocked by administration of a platelet activating factor antagonist before the challenge, suggesting that platelet activating factor was at least partially responsible for the neutrophil priming observed.

The function of neutrophils in a tissue matrix environment may also be very different from that of circulating cells. Various cell-surface receptors [29,30,31] are expressed after stimulation by various mediators, resulting in cell adherence and migration. Neutrophils adherent to extracellular matrix proteins such as fibronectin or laminin have been shown to be capable of a large respiratory burst in response to small quantities of cytokines compared with cells in aqueous suspension. The clinical importance of this observation remains undefined.

As a means of improving granulocyte function after burn injury, the administration of granulocyte–macrophage colony-stimulating factor to thermally injured patients has been studied [32]. In addition to stimulating proliferation of granulocyte and macrophage progenitor cells, this agent increases macrophage phagocytic and cytocidal activity, granulocyte RNA and protein synthesis, granulocyte oxidative metabolism, and antibody dependent cytotoxic killing in mature cells *in vitro*.

Treatment by Granulocyte–macrophage colony-stimulating factor in a small cohort of burned patients [32] increased granulocyte counts by 50% and reduced granulocyte cytosolic oxidative function and myeloperoxidase activity to control levels without changing superoxide production. After treatment was stopped, however, superoxide activity increased compared with untreated burned patients. These findings caution against clinical extrapolation of in-vitro results. A reduction in myeloperoxidase activity may actually be detrimental because bactericidal capability may be compromised, and increased superoxide production could potentiate endothelial cell damage, leading to increased capillary permeability and contributing to the systemic inflammatory response syndrome.

The inability of immunomodulatory drugs to alter significantly changes in immune function after burns may simply represent the inability of single agents to influence the complex and redundant cascade of pathophysiologic events occurring in extensively burned patients.

The clinical signs of infection or a systemic inflammatory response-like syndrome are often indistinguishable from those of uninfected hypermetabolic patients with extensive burns and include hyperthermia, tachycardia, tachypnea, glucose intolerance, and hyperdynamic circulation. Distinguishing between infection, hypermetabolism, and the 'sepsis syndrome' is problematic both clinically with regard to initiating appropriate treatment and investigationally with regard to grouping patients according to the mechanism responsible for the altered physiology.

In an attempt to facilitate earlier identification of infected patients, serum neopterin, which is released by activated mononuclear leukocytes, was serially measured in burned patients and correlated with the development of infection [33]. Elevated levels correlated with the presence of infection and were sometimes elevated for up to 10 days before treatment was started. Because of the similarity in clinical presentation of infections and inflammatory or hypermetabolic conditions, a laboratory tool that permits accurate and reliable separation of the entities would be extremely useful.

Conclusion

Despite significant improvement in the survival of thermally injured patients, infectious complications continue to be a significant source of morbidity and mortality. Control of invasive burn wound infection by effective topical antimicrobial agents and timely excision and skin grafting of the burn wound have been associated with changes in the predominant sites and types of infection. Strict isolation techniques and improved wound care have successfully controlled infections due to Gram-negative organisms. These infections have been supplanted by infections caused by true fungi, yeast, and multiple antibiotic resistant bacteria.

Improvements in fluid management, wound care, and nutritional support have markedly reduced early mortality from thermal injury and prolonged the hospital course of nonsurvivors. Thus, increased emphasis has been placed on elucidation of the systemic inflammatory response syndrome and multiple system organ failure as potential targets for future therapeutic interventions.

Despite a fervor of research activity, the complexity of the pathophysiologic events causing the systemic inflammatory response has limited the success of interventions intended to ameliorate cellular injury. Continued efforts to define the roles of the various immunologic cell populations and their cytokine mediators in the initiation and propagation of this response may eventually permit

selective interruption of the deleterious effects of this redundant cascade.

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